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13th Belgian Symposium on the Integration of Molecular Biology / Advances into Oncology Clinical Practice

23/11/2019

Radioisotopic Therapies and Theragnostics in endocrine tumors: an evolving field

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JULES BORDET INSTITUTE

THERAGNOSTICS: therapeutic+diagnostic

- same/similar pharmacological agents can be used for Dx and Tx
- Greek: θεραπεία (to treat) + γνώσις (knowledge)
- standard practice in NM for over 70y
- this merging enables precision and personalized Medicine: «right Tx, right patient, right time, right dose»

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THERAGNOSTICS

Personalized medicine

From Wikipedia, the free encyclopedia
(Redirected from Theranostics)

Personalized medicine, precision medicine, or **theranostics** is a medical model that separates people into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease.[1] The terms personalized medicine, precision medicine, **stratified medicine** and P4 medicine are used interchangeably to describe this concept[1][2] though some authors and organisations use these expressions separately to indicate particular nuances.[2]

While the tailoring of treatment to patients dates back at least to the time of Hippocrates,[3] the term has risen in usage in recent years given the growth of new diagnostic and informatics approaches that provide understanding of the molecular basis of disease, particularly genomics. This provides a clear evidence base on which to stratify (group) related patients.[1][4][5]

Part of a series on
Genetics

Key components
Chromosome · DNA · RNA
Genome · Heredity · Mutation
Nucleotide · Variation
Outline · Index

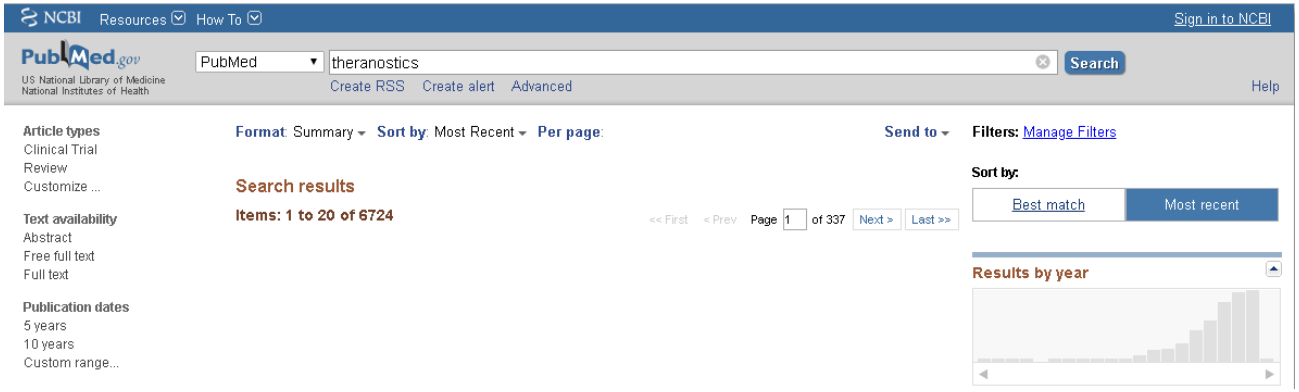
History and topics
Introduction · History
Evolution (molecular)
Population genetics
Mendelian inheritance
Quantitative genetics
Molecular genetics

Research
DNA sequencing
Genetic engineering
Genomics (template)
Medical genetics
Branches of genetics

Personalized medicine
Personalized medicine

Biology portal

V · T · E



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THERAGNOSTICS IN NM

- a diagnostic agent (imaging) will determine if a patient would benefit from the therapeutic agent → whole body imaging to assess entire tumor burden
- receptor binding and internalisation → selective uptake by tumor cells → high T-nTR → as high as possible radiation doses to tumor cells, as low as possible to critical organs
- effective and irreversible lesion toxicity with minimal side effects
- favourable PK to allow repeated therapies

COMMON THERAGNOSTIC AGENTS IN NM

CLINICAL INDICATION	TARGET	DIAGNOSTIC AGENT	THERAPEUTIC AGENT
hyperthyroidism/thyroid cancer	NIS	^{123}I-iodide, ^{131}I-iodide	^{131}I-iodide
NET & NE DT	SSTR	^{68}Ga-DOTATATE	^{177}Lu-DOTATATE (Lutathera)
adrenal medullary tumor	VMAT2	^{123}I-MIBG, ^{131}I-MIBG	^{131}I-MIBG (Azedra)
bone metas from prostate cancer	hydroxyapatite	^{99m}Tc-MDP	^{223}Ra-Cl (Xofigo)
NHL	CD20	^{111}In-ibritumomab	^{90}Y-ibritumomab (Zevalin)
prostate cancer	PSMA	^{68}Ga-PSMA 11	^{177}Lu-PSMA 617

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Ballinger JR: *BJR* 2018

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THERAGNOSTICS IN NETs

- **DIAGNOSTIC IMAGING (β+ PET)**
  ^{68}Gallium-DOTA-agonists
  - staging, patient selection for Tx (SSA/PRRT)

- **THERAPY (β-)**
  ^{177}Lutetium-DOTA-agonists
  - Peptide Receptor Radionuclide Therapy
  - Lu: agent of choice (reduced radiation dose to COs, quantification)

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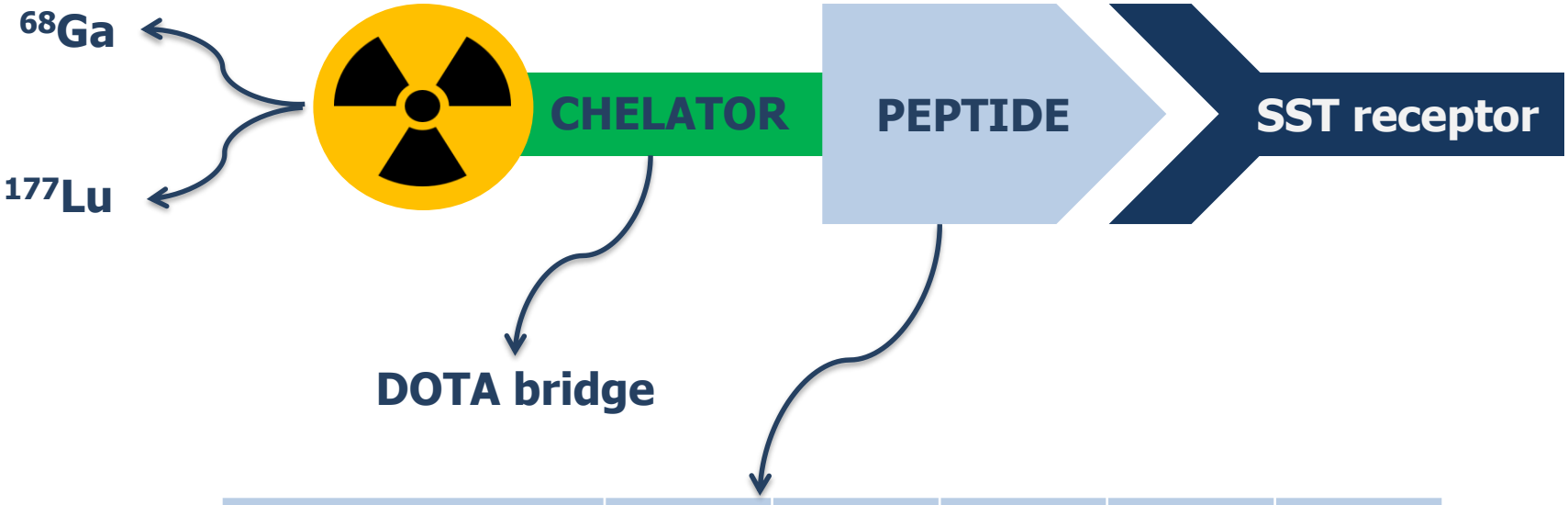
THERAGNOSTIC TWINS



PEPTIDES	sst_1	sst_2	sst_3	sst_4	sst_5
native SS_{28aa}	5,2	2,7	7,7	5,6	4,0
octreotide	>10.000	2.0	187	>1.000	22
lanreotide	180	0,54	14	230	17
pasireotide	9,3	1	1,5	>100	0,16
DOTA-Tyr^3-octreotide	>10.000	14	880	>1.000	393
DOTA-lanreotide	>10.000	26	771	>10.000	73
DOTA-Tyr^3-octreotate	>10.000	1,5	>1.000	453	547

IC_{50} in nM

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de Herder WW *et al: Endocrine-Related Cancer 2003*
Reubi JC: *Endocr Rev* 2003
Reubi JC *et al: Ann NY Acad Sci* 1994

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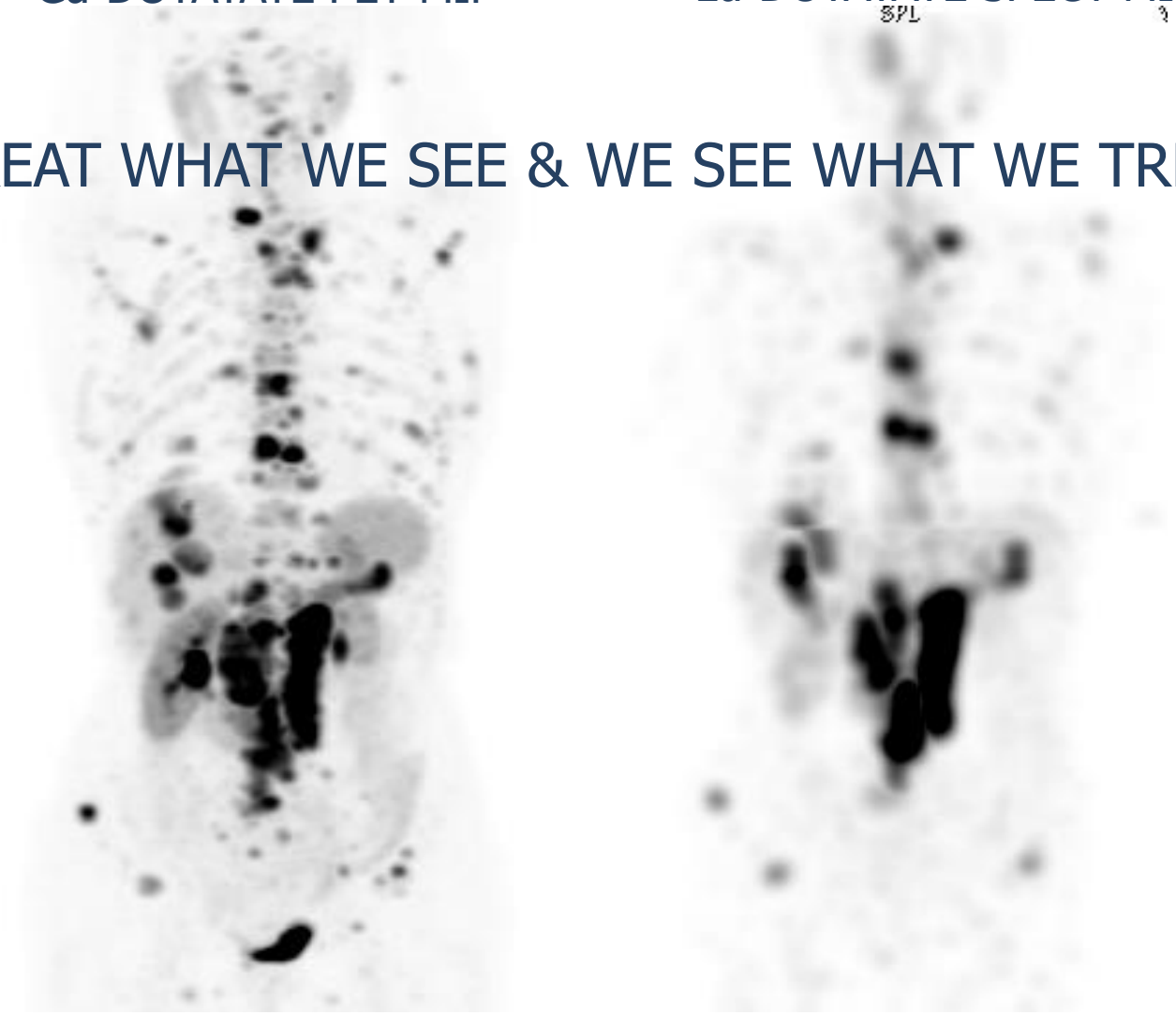
THERAGNOSTIC TWINS

^{68}Ga-DOTATATE PET MIP

^{177}Lu-DOTATATE SPECT MIP



WE TREAT WHAT WE SEE & WE SEE WHAT WE TREAT...

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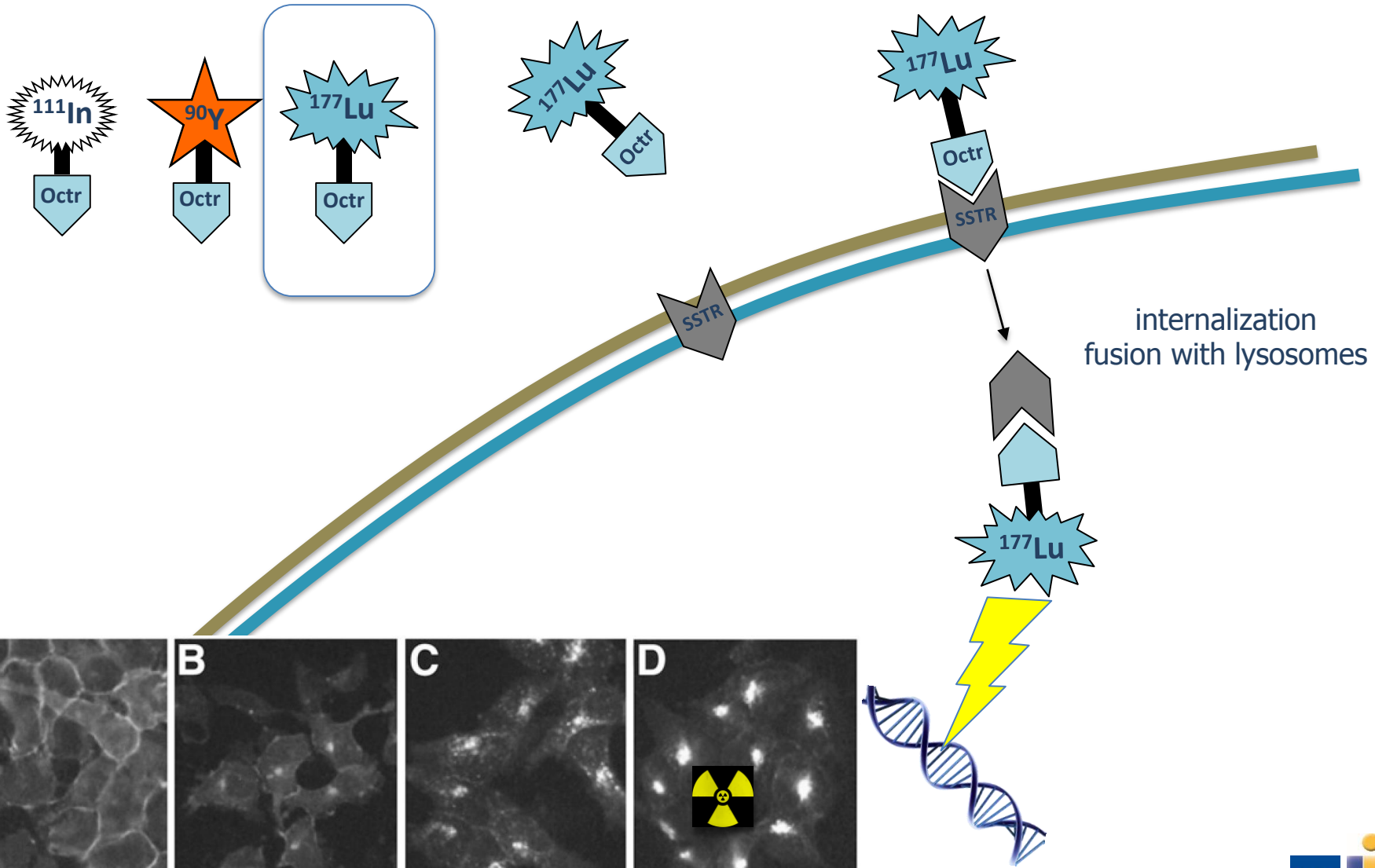
PRRT PRINCIPLE



Waser B *et al.*: *JNM* 2009

IAEA
International Atomic Energy Agency

EANM®
European Association of Nuclear Medicine

SNMMI

Eur J Nucl Med Mol Imaging (2013) 40:800–816
DOI 10.1007/s00259-012-2330-6

GUIDELINES

The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

European ENETS Neuroendocrine Tumor Society

Conference Report

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Peptide Receptor Radionuclide Therapy with Radiolabelled Somatostatin Analogues

Neuroendocrinology 2017;105:295–309
DOI: 10.1159/000475526

Received: December 12, 2016
Accepted after revision: April 6, 2017
Published online: April 13, 2017

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Bodei L *et al*: joint **IAEA/EANM/SNMMI guidelines** *EJNMMI* 2013
Hicks RJ *et al*: **ENETS guidelines** *Neuroendocrinology* 2017

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PRRT INDICATIONS & CONTRAINDICATIONS

- WD NETs:
  - overexpressing SSTR (uptake > hepatic parenchyma)
  - G1, G2, G3 (if SSTR+)
  - GEP, lung or other origin, PHEOs/PGLs, MTC, MCC
- metastatic, unresectable
- progressive (clinically, morphologically, SSTR imaging)

- Hb<8g/dL, PLT<75×10^9/L, WBC<2×10^9/L
- GFR<50 mL/min
- mismatch FDG+/SSTR-

- HF NYHA grade III/IV
- $bilirubin_{total}$>3×ULN, alb<25g/L ± PT>1.5×ULN
- pregnancy/lactation, no cooperation
- ECOG≥2, poor survival expectancy

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Hicks RJ *et al*: **ENETS guidelines** *Neuroendocrinology* 2017

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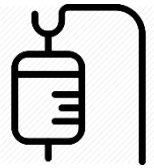
THERAPEUTIC SCHEME



- suspend SSAs (LA/SA), re-introduction SSAs d+1 permissible
- *iv*, q6-12w
- hospitalisation in dedicated rooms, radioprotection instructions

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Bodei L *et al.*: joint **IAEA/EANM/SNMMI guidelines** *EJNMMI* 2013
Hicks RJ *et al.*: **ENETS guidelines** *Neuroendocrinology* 2017

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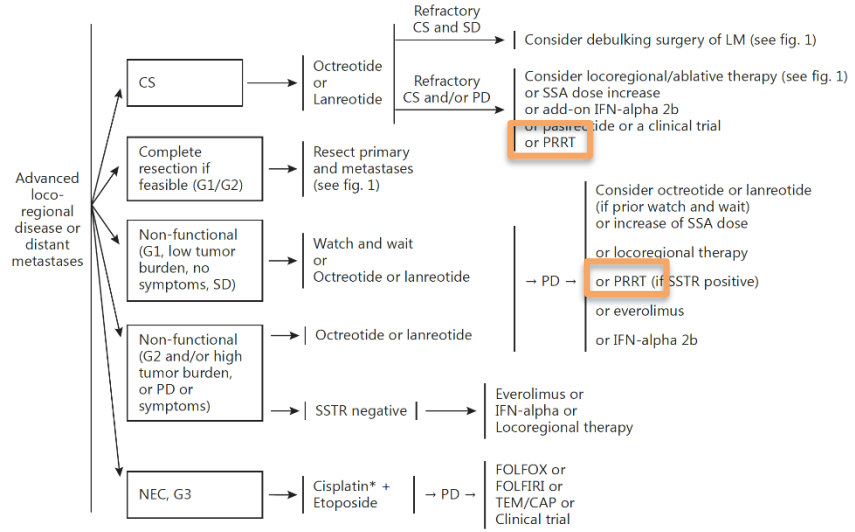
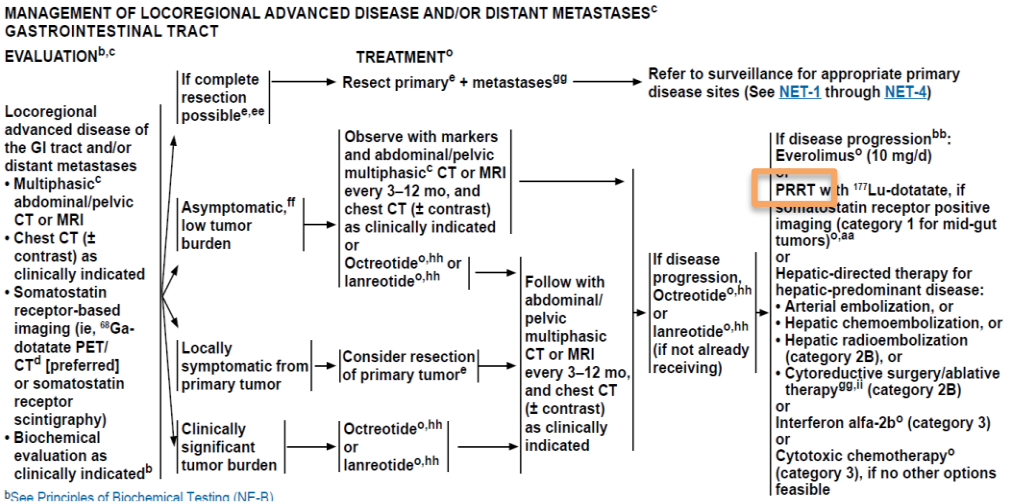
PLACE OF PRRT IN siNETs





- locoregional advanced ± distant metas, progressive after SSA
  vs everolimus
  vs hepatic-directed therapy for hepatic only/dominant disease
  vs interferon alfa-2b
  vs cytotoxic chemotherapy

- CS refractory to SSA ± progressive disease

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Pavel M*et al*: *Neuroendocrinology* 2016, NCCN GUIDELINES 2.2018

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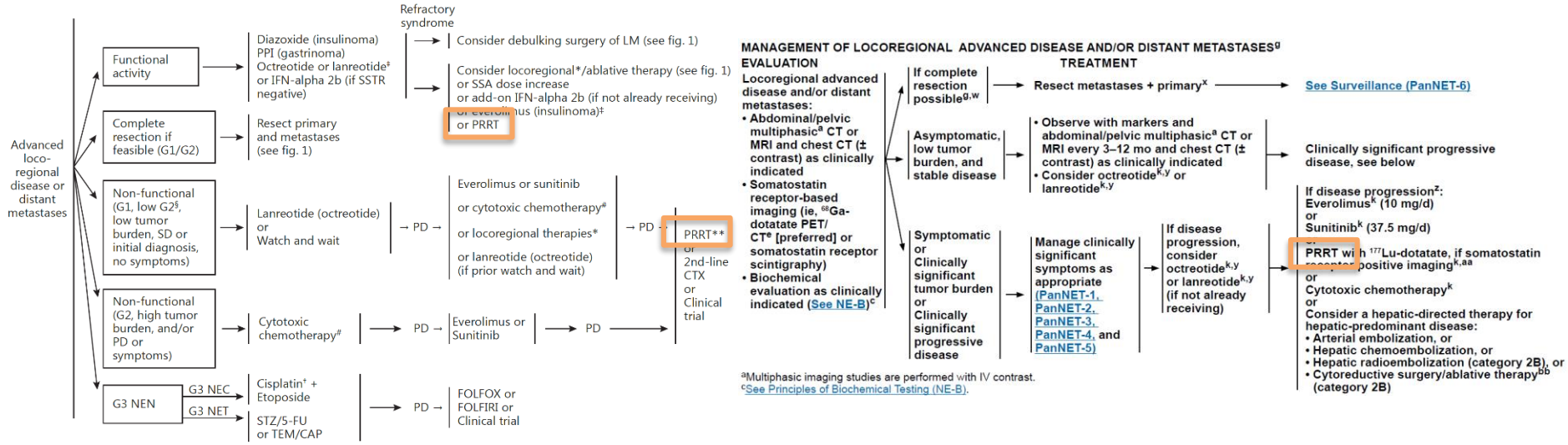
PLACE OF PRRT IN panNETs



- locoregional advanced ± distant metas, progressive (after SSA)
  vs everolimus
  vs sunitinib
  vs cytotoxic chemotherapy
  vs hepatic-directed therapy for hepatic only/dominant disease

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Pavel M*et al*: *Neuroendocrinology* 2016, NCCN GUIDELINES 2.2018

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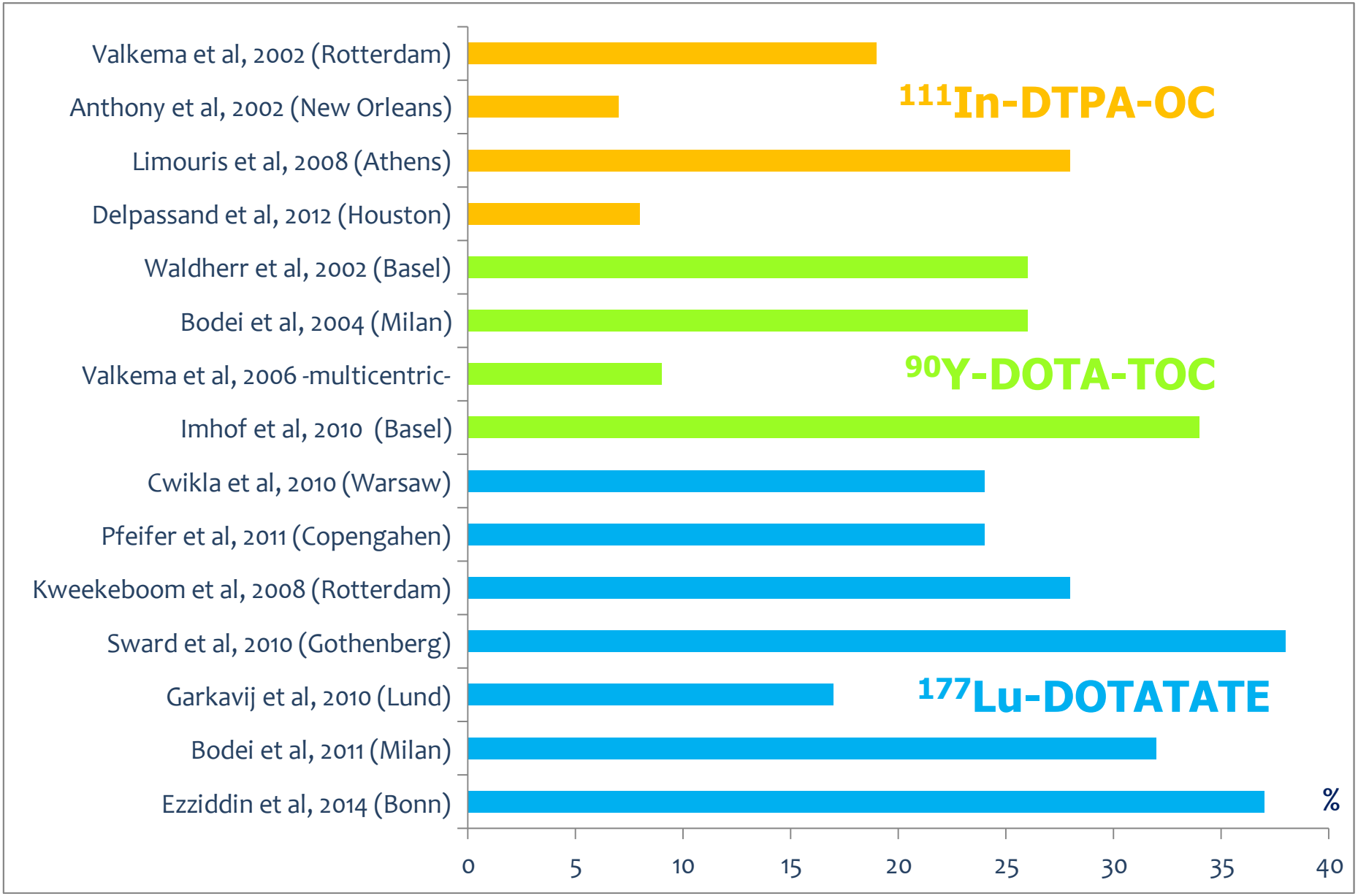
EFFICACY / OR: CR+PR



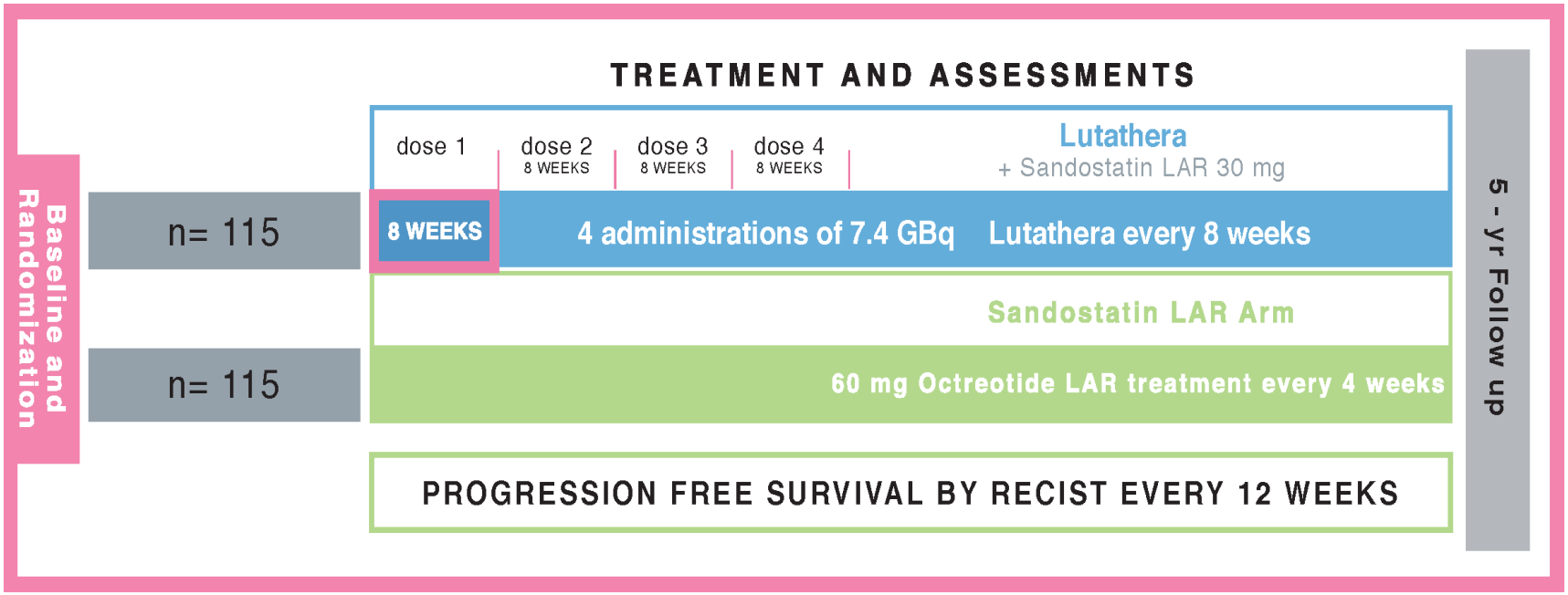
EFFICACY: PFS/OS

Trial	Therapeutic Agent	pts	PFS (m)	OS (m)
Valkema *et al*, 2002	^{111}In-DTPA-OC	32	-	12
Delpassand *et al*, 2012	^{111}In-DTPA-OC	40	-	22
Valkema *et al*, 2006	^{90}Y-DOTA-TOC	58	29	37
Bushnell *et al*, 2010	^{90}Y-DOTA-TOC	90	16	27
Cwikla *et al*, 2010	^{90}Y-DOTA-TOC	58	17	22
Pfeifer *et al*, 2011	^{90}Y-DOTA-TOC	53	29	-
Kwekkeboom *et al*, 2008	^{177}Lu-DOTATATE	310	33	46
Bodei *et al*, 2011	^{177}Lu-DOTATATE	42	-	36
Ezziddin *et al*, 2014	^{177}Lu-DOTATATE	74	26	55
Kouvaraki *et al*, 2004	STZ+5-FU+DOXORUBICIN	84	39	18/37
Kulke *et al*, 2009	TMZ	53	34	14/35
Strosberg *et al*, 2010	TMZ+CAPECITABINE	30	70	38/-
Chan *et al*, 2013	TMZ+BEVACIZUMAB	15	33	14/42
Chan *et al*, 2013	TMZ+EVEROLIMUS	43	40	15/-
Yao *et al*, 2011	EVEROLIMUS	207	5	11/-
Raymond *et al*, 2011	SUNITINIB	86	9	11/-

NeuroEndocrine Tumors ThERapy: NETTER-1

- first prospective, multicentric, randomized φIII metastatic/unresectable SSTR+ midgut NETs G1/G2 progressive (RECIST 1.1/3y) under standard OC (30-40 mg) Tx

- Sandostatine LAR 60mg *vs*
4x ^{177}Lu-DOTATATE ca + Sandostatine LAR 30mg



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Strosberg J *et al.*: *NEJM* 2017

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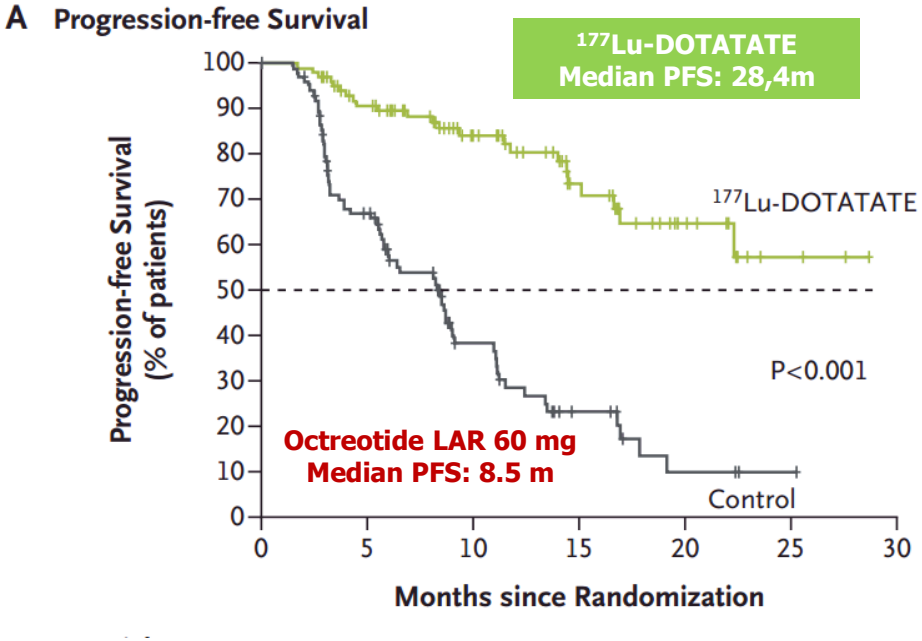
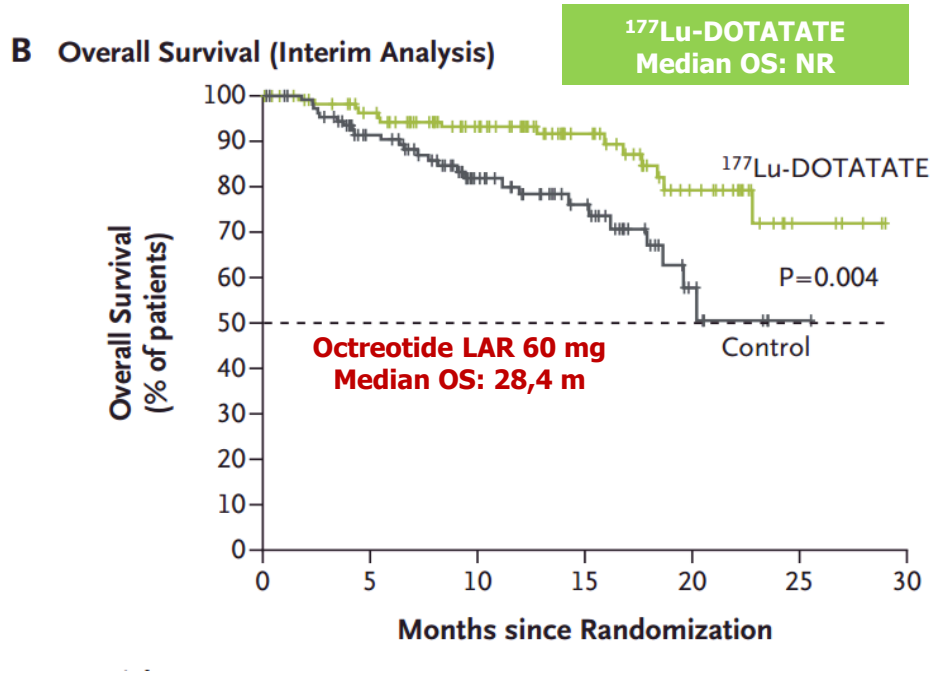
EFFICACY - PFS/OS (n: 229)





INSTITUT JULES BORDET INSTITUUT

Strosberg J *et al.*: ENETS 2019

ULB iris

EFFICACY - OR (n: 201)

TYPE OF RESPONSE	PRRT (n=101)	SSA (n=100)
Complete Response (n)	1	0
Partial Response (n)	18	3
Objective Response (n, %)	19 (19%)	3 (3%)
Progressive Disease (n, %)	5 (5%)	27 (27%)
Stable Disease (n, %)	77 (77%)	70 (70%)

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Strosberg J *et al.*: NEJM 2017

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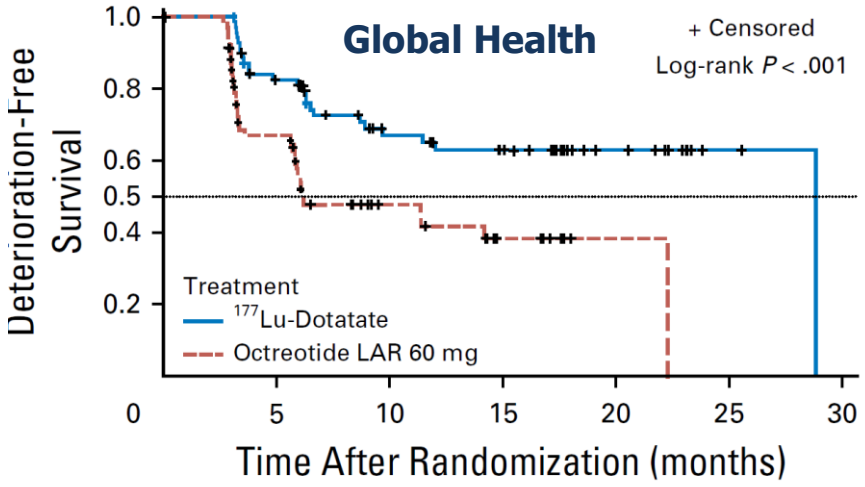
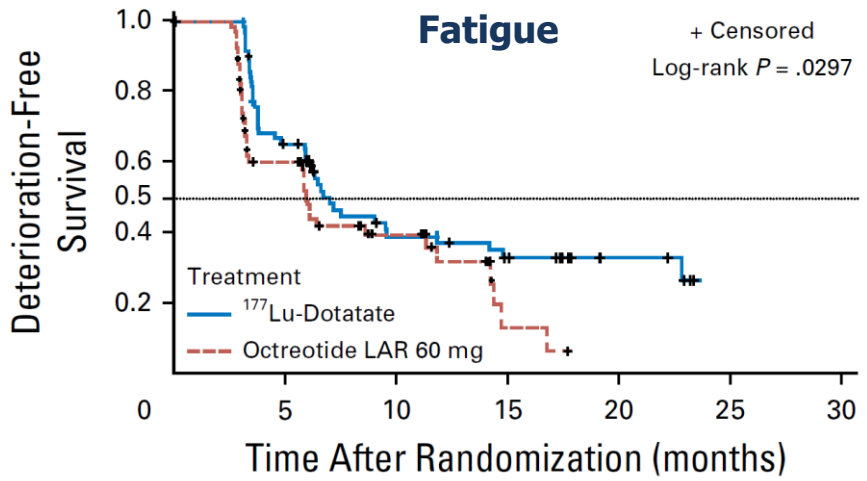
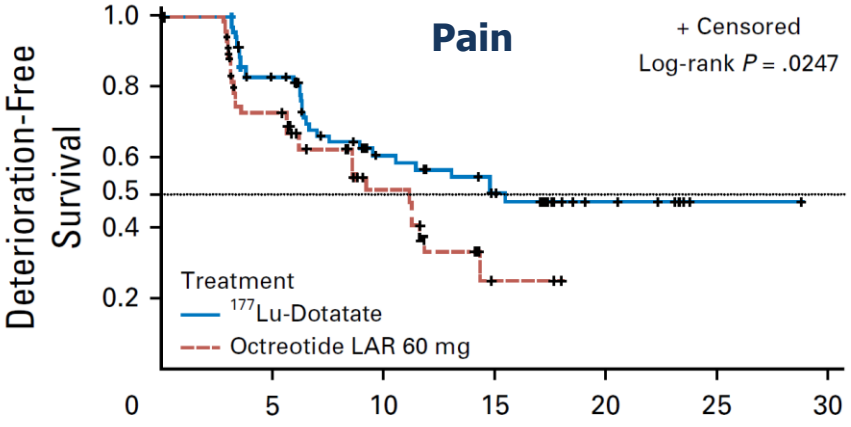
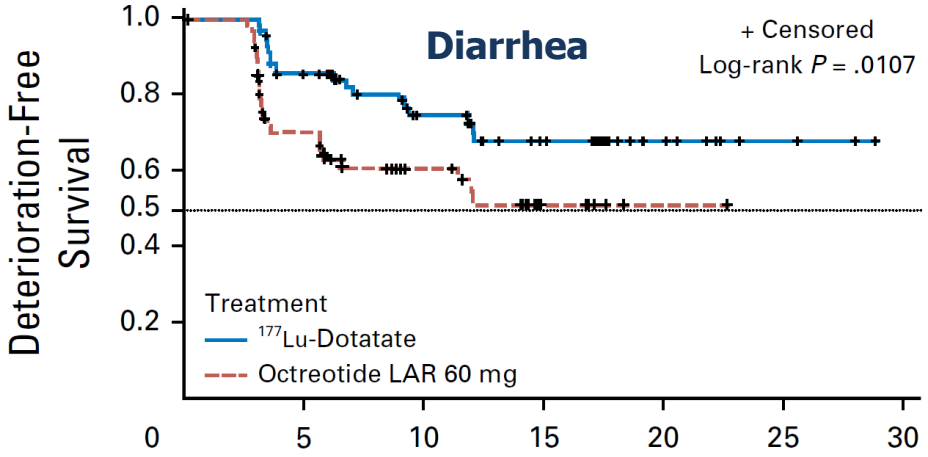
EFFICACY - QoL (n: 231)









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Strosberg J *et al.*: *JCO* 2018

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PRRT TOXICITY

❖ DOSE DEPENDENT

ACUTE

>nausea/vomiting, fatigue
>abdominal pain/disconfort
>carcinoid crisis: ≤1%

SUBACUTE/CHRONIC

>G3/G4 hematological:≤11%
(nadir: 6th-8thw pi)
>G1 alopecia: 65-70%

CHRONIC

>G3/G4 renal:<3%
(not an issue with ^{177}Lu-PRRT)

❖ DOSE INDEPENDENT

MDS

>rare: ≤3% (MDS: 2%/AL:1%)
>stochastic event: unidentified individual susceptibilities
>no correlation with administered activities/cycles
>mutational events induced by sequentional cytotoxic Tx

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Strosberg J *et al.*: NEJM 2017, Bodei L *et al.*: *Sem NM* 2016, Bodei L *et al.*: *EJNMMI* 2015
de Keizer B *et al.*: *EJNMMI* 2008, Sabet A *et al.*: *JNM* 2013, Kwekkeboom DJ *et al.*: *JCO* 2008

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RISK FACTORS FOR PRRT TOXICITY

❖ DOSE DEPENDENT	❖ DOSE INDEPENDENT
HEMATOLOGIC >extensive BM infiltration >poor baseline values >poor baseline renal function >age >previous EBRT **RENAL** >diabetes, hypertension >previous nephrotoxic agents	**MDS** >previous myelotoxic agents: alkylating/topoisomerase II-i >previous EBRT (pelvis?)

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Bodei L *et al.*: E*RC* 2016, Bergsma H *et al.*: *EJNMMI* 2016

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PREDICTORS OF OUTCOME

- high baseline uptake on Ga-DOTA PET: SSTR expression
  > SUVmax≥25: higher tumor doses

- primitive origin
  > panNETs: OR~40-50%
  > rectNETs: OR~70%
  > siNETs: responses (SD) reflect rather low aggressive behaviour

- progressive ⇩ of uptake (^{68}Ga-DOTA PET & ^{177}Lu-DOTA SPECT)
  progressive reduction of CgA

- poor outcomes: high tumor burden with bulky liver mets
  bone/peritoneal mets
  ECOG ≥2

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Khan S *et al*: *JNM* 2011, Kong G *et al*: *EJNMMI* 2018, Severi S *et al*: *EJNMMI* 2013
Ezziddin S *et al*: *Clin Nuc Med* 2012, Haug A *et al*: *JNM* 2010, Kwekkeboom DJ *et al*: *JCO* 2008

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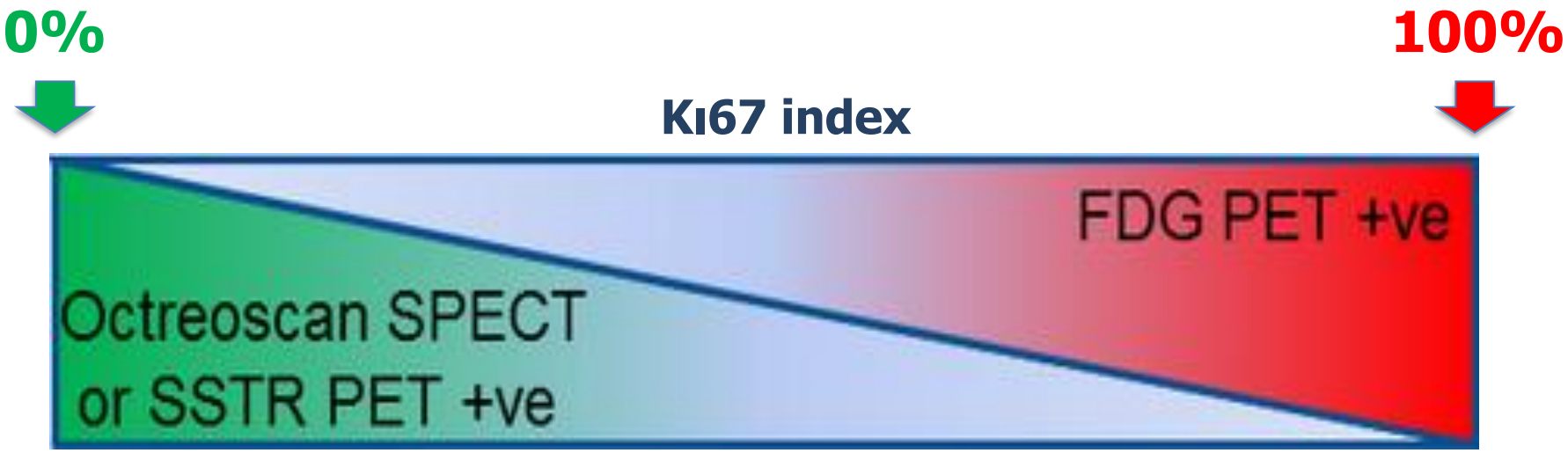
STRATEGIES TO IMPROVE PRRT EFFICACY

- OPTIMAL SELECTION OF PATIENTS
  > combined MI imaging
  > no mismatch FDG+/SSTR-



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Hofman MS *et al*: *Discov Med* 2012, Karfis I *et al*: manuscript accepted on Oncotarget

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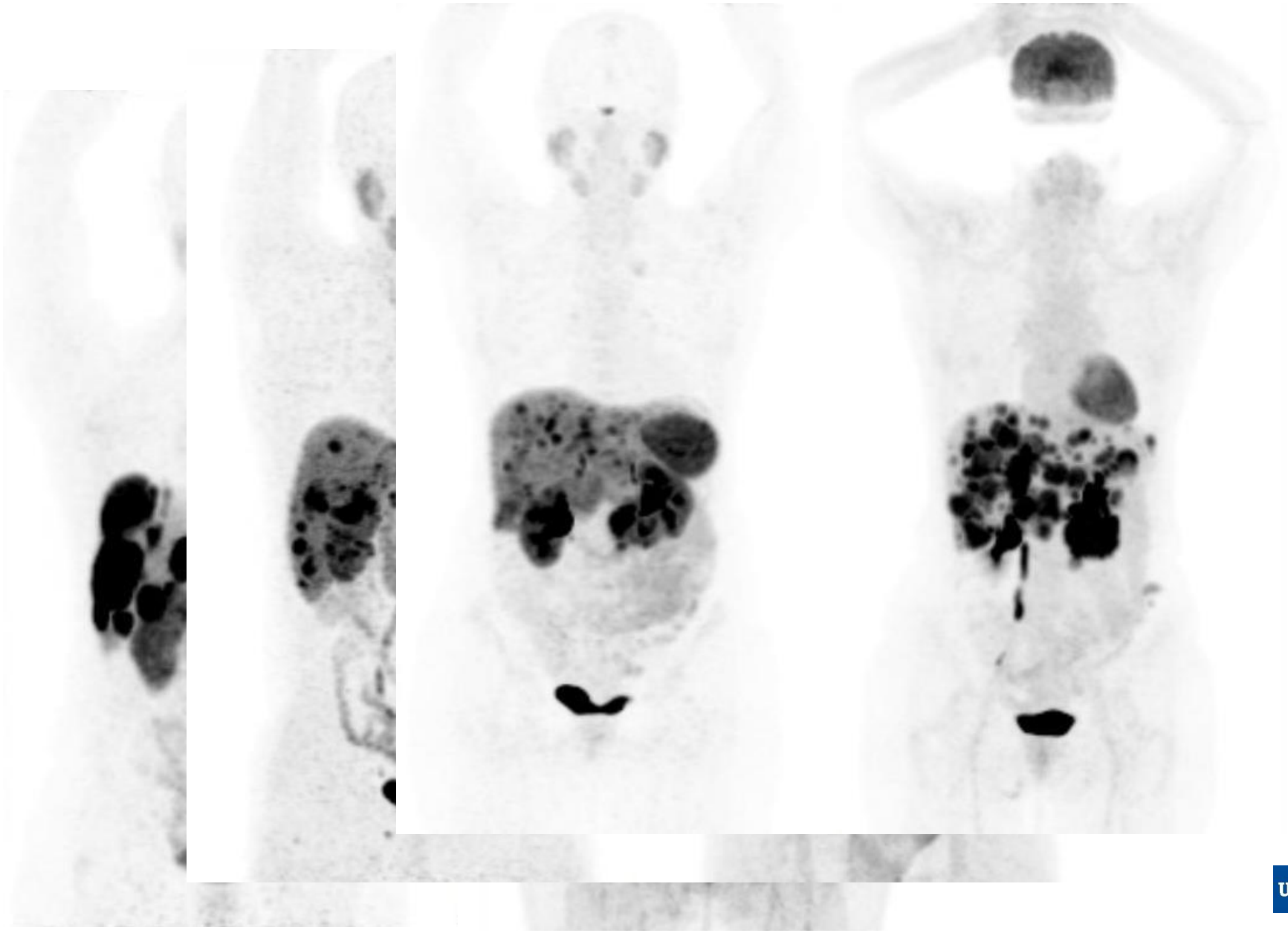
MOLECULAR IMAGING PHENOTYPE IN NETs



STRATEGIES TO IMPROVE PRRT EFFICACY

- COMBINATION WITH CHEMOTHARAPY (Cap/Tem)
  - Peptide Receptor Radionuclide Chemo-Therapy (PRRCT)
  - in selected patients with FDG-avid, concordant lesions

- 65pts GEP-NETs, mPFS: 31m, CR:16%, PR:41%, SD:37%

	Hematological toxicity grade			
	1	2	3	4
Short-term toxicity (up to 6 months)				
PRRT+C (n = 28)				
Neutropenia	5 (18)	2 (7)	1 (3.5)	0
Anemia	21 (75)	0	0	0
Thrombocytopenia	16 (57)	1 (3.5)	0	0
PRRT+C+T (n = 37)				
Neutropenia	10 (27)	3 (8)	0	0
Anemia	24 (65)	5 (13.5)	0	0
Thrombocytopenia	21 (57)	8 (21.5)	0	0

	Hematological toxicity grade			
	1	2	3	4
Long-term toxicity				
PRRT+C (6–60 months) (n = 28)				
Neutropenia	1 (3.5)	0	0	0
Anemia	11 (39)	0	1 (3.5)	0
Thrombocytopenia	2 (7)	0	0	1 (3.5)
PRRT+C+T (6–36 months) (n = 37)				
Neutropenia	2 (5.4)	2 (5.4)	1 (2.7)	0
Anemia	10 (27)	1 (2.7)	4 (10.8)	0
Thrombocytopenia	12 (32.4)	1 (2.7)	0	1 (2.7)

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Lewin J et al: *EJNMMI* 2017

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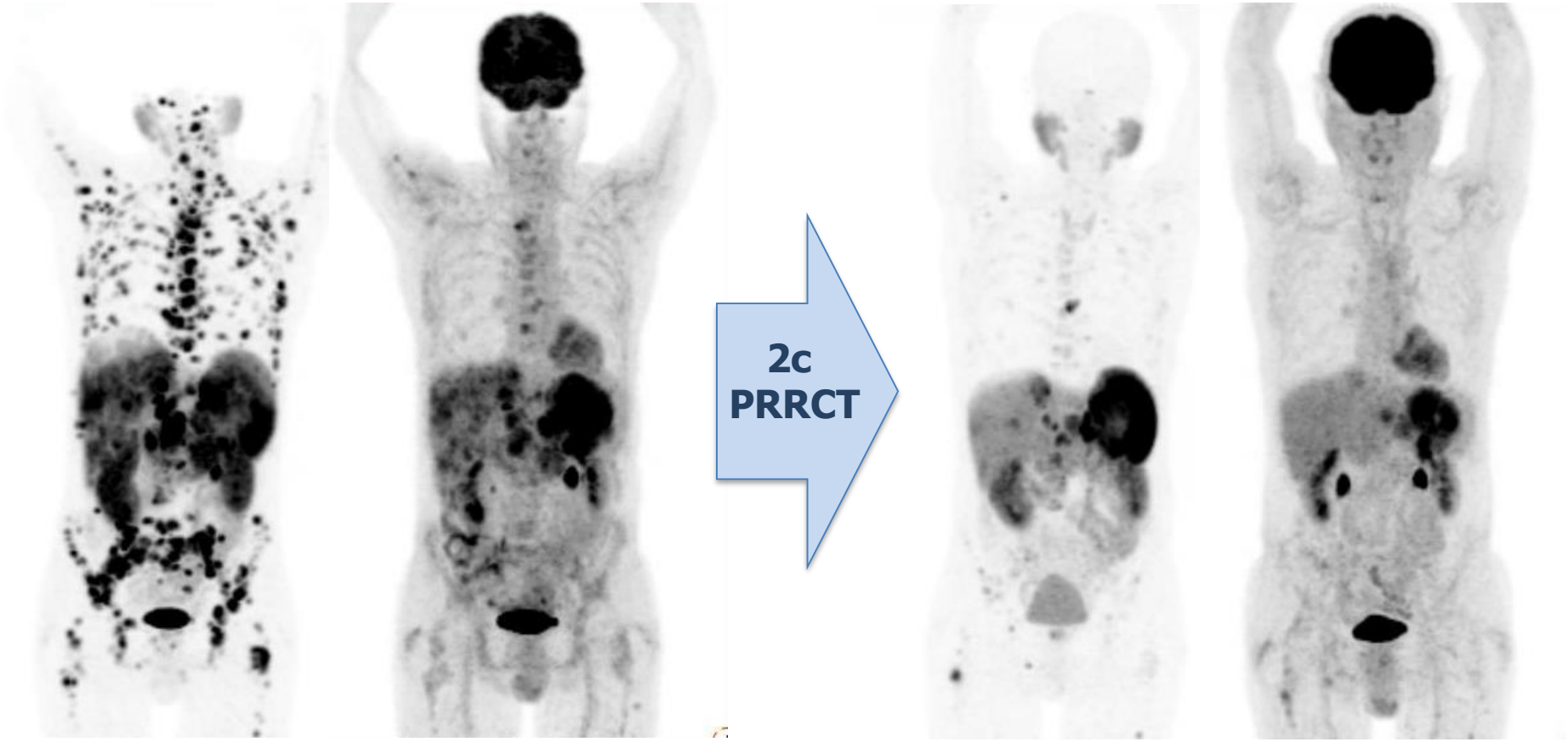
PRRCT

- 58y panNET highG2 (Ki67:15%), second line PRRT after SSAs

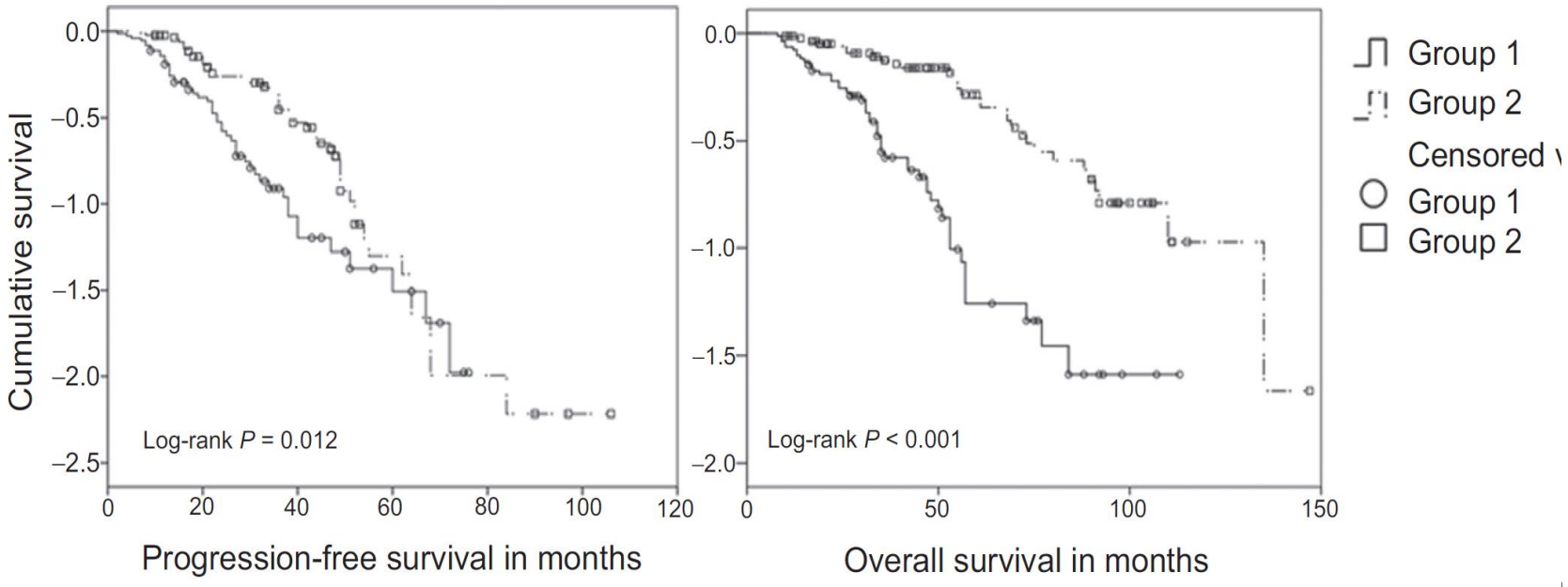


STRATEGIES TO IMPROVE PRRT EFFICACY

- COMBINATION WITH SSAs (during PRRT ± maintenance)

- 168pts GEP-NETs G1-2: 81 PRRT vs 87 PRRT+SSA
  mPFS: 27m vs 48m,
  mOS: 47m vs 91m

  enhancement of the antiproliferative effect by adding SSA to PRRT??



Yordanova A et al: *Clin Canc Res* 2018

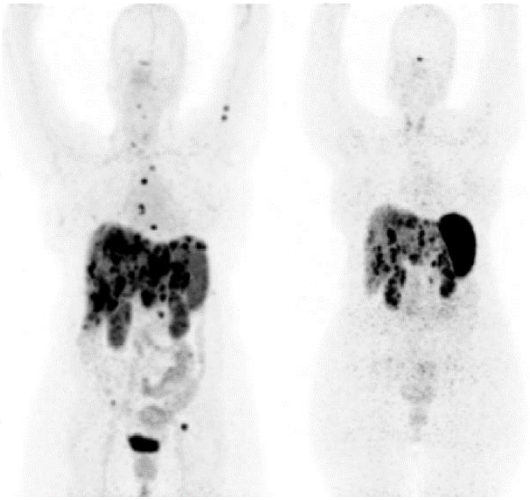
STRATEGIES TO IMPROVE PRRT EFFICACY

- intra-arterial PRRT: liver only / dominant disease
- alpha-emittors: ^{225}Ac

^{225}Ac-DOTATATE Therapy $N = 24$

Site of primary tumour	Stable disease on ^{177}Lu-DOTATATE therapy ($N = 12$)					Site of primary tumour	Progressive disease on ^{177}Lu-DOTATATE therapy ($N = 12$)				
	CR	PR	MR	SD	PD		CR	PR	MR	SD	PD
Pancreatic NETs ($N = 8$)	0	5	2	0	0	Pancreatic NETs ($N = 8$)	0	3	1	1	0
Foregut ($N = 3$)	0	3	0	0	0	Foregut ($N = 4$)	0	1	1	0	0
Midgut ($N + 2$)	0	0	1	0	0	Midgut ($N = 1$)	0	1	0	0	0
Hindgut ($N = 0$)	0	0	0	0	0	Hindgut ($N = 1$)	0	1	0	0	0
Unknown primary ($N = 1$)	0	0	1	0	0	Unknown primary ($N = 4$)	0	1	0	2	0
Total (N)	0	8	4	0	0	Total (N)	0	7	2	3	0

CR complete remission, *PR* partial response, *MR* minimal response, *SD* stable disease, *PD* progressive disease



- antagonists: OPS201 (DOTA-JR11)
  >no internalisation
  >bind to more receptor sites → potentially higher tumor doses
- neoadjuvant PRRT: tumor downsizing

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Limouris GS *et al*: *Clin Nucl Med* 2016, Ballal S *et al*: *EJNMMI* 2019, Nicolas GP *et al*: *JNM* 2017, Sowa-Staszczak A *et al*: *EJNMMI* 2011

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re-Tx IS POSSIBLE

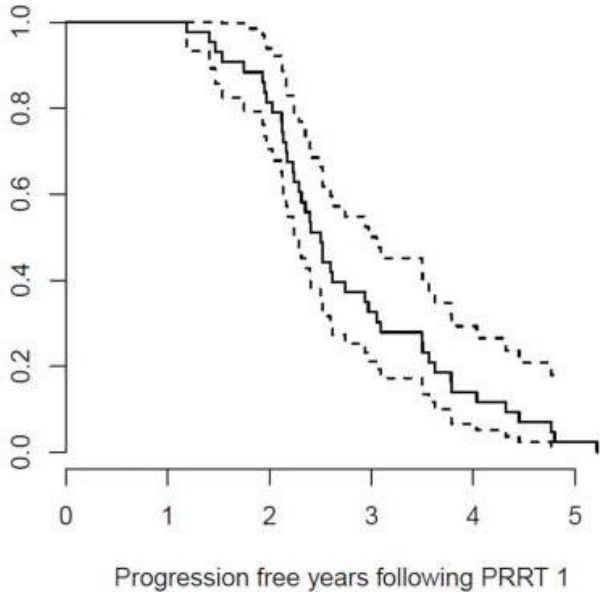
- under conditions:
  - second progression >1y
  - no mismatch between FDG/Ga-DOTA
  - acceptable hematological reserves, ECOG<2
  - acceptable dosimetric data of PRRT1
  - response on PRRT1

- PRRT2 less effective than PRRT1:
  - poorer performance status
  - dedifferentiattion? radioresistance?
  - more extensive tumor load→suboptimal absorbed doses

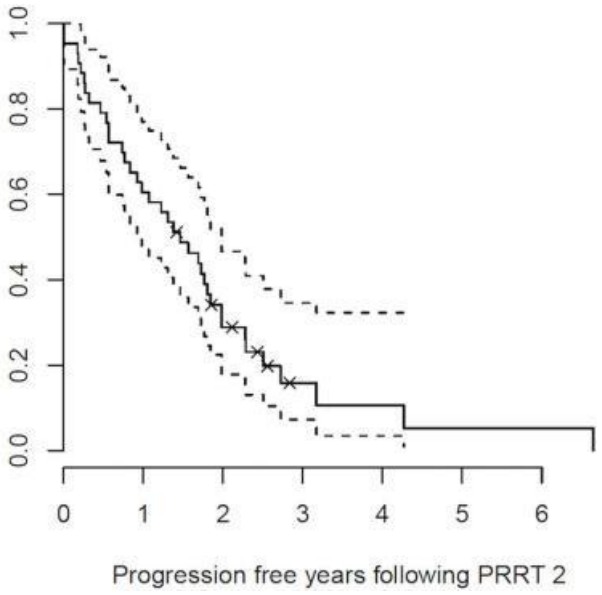
re-Tx IS POSSIBLE

- 47 NET pts G1/G2, ^{90}Y-PRRT 2000-2012

PRRT1 N=47	**PRRT2** N=44
>mPFS1: 30m	>mPFS: 17.5m
>PR:10, SD:37	>PR:7, SD:26, PD:11
>nephrotox:1, G$^{3/4}$myelotox:3	>nephrotox:7, G$^{3/4}$myelotox:17



m2,6y
[1,5-7,1y]



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Vaughan E et al: *Br J Radiol* 2018

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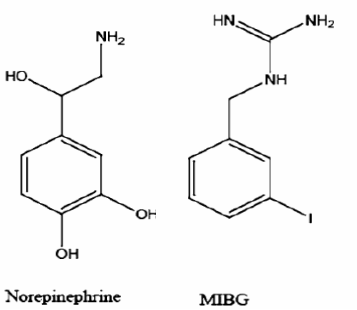
PHEOs & PARAs: theragnostic imaging agents

- MIBG (=**m**eta**i**odo**b**enzyl**g**uanidine) SPECT
  - iodinated guanidine analoge, structurally similar to NA
  - produced from dopamine, stored on the presynaptic vesicles
  - historical MI-gold standard
  - non metastatic, sporadic PHE: Se: 76-100%, Sp: 95-100%
    metastatic, hereditary PHE: Se: 52-75%, Sp: 90-95%



- Ga-DOTA-SSA PET
  - pooled Se: 93% [95% CI: 91-95%]

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Sisson JC *et al*: *NEJM* 1981 & 1984, Timmers HJ *et al*: *J Clinical Endocrinology Metabolism* 2009
Taieb D *et al: Endoc Rel Cancer* 2019

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PHEOs & PARAs: ^{131}I-MIBG

- in metastatic MIBG+ patients
- pooled objective responses: CR/PR: 25%, SD: 52%
- small doses over a long period vs high doses + autologous stem-cell transplantation
- myelotoxocity: thrombocytopenia/leukopenia (G3/G4: 85%), 4%: MDS
  hypothyroidism (15-20%), sialadenitis,

Trial	cycles, responses	pts	PFS	OS
Sisson *et al*, 1984	2-4, PR:2/SD:3	5	-	-
Charbonnel *et al*, 1988	1-8, PR:3	12	-	-
Krempf *et al*, 1991	2-11, PR:5/SD:7	15	-	48%@22m
Mukherjee *et al*, 2001	1-7, PR:8/SD:4	15	-	-
Safford *et al*, 2003	1-6, CR:8/pr:8	33	-	4,7y
Gonias *et al*, 2009	1-4, CR:8/PR:8/SD:24	49	-	64%@5y
Castellani *et al*, 2010	1-12, CR:2/PR:3/SD:6	24	-	-
Fishbein *et al*, 2012	1-4	5	23m	-
Pryma *et al*, 2019	1-4, OR: 59/68	68		36,7

PHEOs & PARAs: PRRT

- mostly retrospective case series
- >90% clinical improvement, overall ~70-80% achieve SD+PR
- response rates seemed to be lower than NET patients

Trial	Therapeutic Agent, c	pts	morphol responders or SD	PFS (m)	OS (m)
Kolasinska-Cwikla *et al*, 2019, P	^{90}Y-DOTATATE, 2-5c	13	10/13	35	68
Vyakaranam *et al*, 2019	^{177}Lu-DOTATATE, 3-11c	22	22/22	21,6	49,6
Zandee *et al*, 2019	^{177}Lu-DOTATATE, 4c	30	27/30	30	-
Yadav *et al*, 2019	^{177}Lu-DOTATATE+Chemo, 2-8c	25	21/25	32	-
Kong *et al*, 2017	^{177}Lu-DOTATATE+Chemo, 1-4c	20	15/20	39	-
Nastos *et al*, 2017	^{177}Lu-/^{90}Y-DOTATATE+Chemo, 1-4c	13	13/13	38,5	60,8
Estevao *et al*, 2015	^{177}Lu-DOTATATE, 3c	14	10/14	-	-
Puranik *et al*, 2015, P	^{177}Lu-/^{90}Y-DOTATATE/TOC, 2-4c	9	9/9	-	-
Imhof *et al*, 2011, P	^{90}Y-DOTATOC, 1-10c	39	-	-	-
Forrer *et al*, 2008	^{177}Lu-/^{90}Y-DOTATOC, 2-4c	28	20/28	-	-
van Essen *et al*, 2008	^{177}Lu-DOTATATE, 4c	12	8/12	-	-

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Satapathy S *et al*: *Clin Endocrinol* 2019

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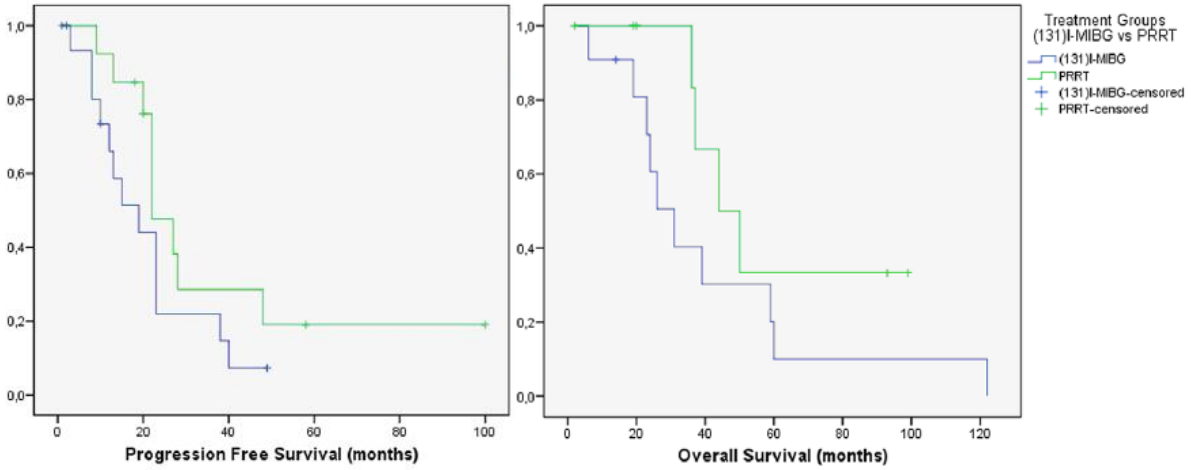
WHAT TO CHOOSE?

- retrospective study of 22pts with progressive metastatic P&P
- 11 MIBG vs 11 ^{90}Y-/^{177}Lu-PPRT

All patients	(131)I-MIBG	PRRT	P-value
Overall survival (months)	41.2 ± 10.4	60.8 ± 11.1	0.09
Progression free survival (months)	20.6 ± 3.4	38.5 ± 9.4	0.10



- PRRT: safer toxicity profile (trends)
- PRRT: no need for Tx interruption, no need for thyroid blockade, better tolerance

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Nastos K *et al*: *JSO* 2017

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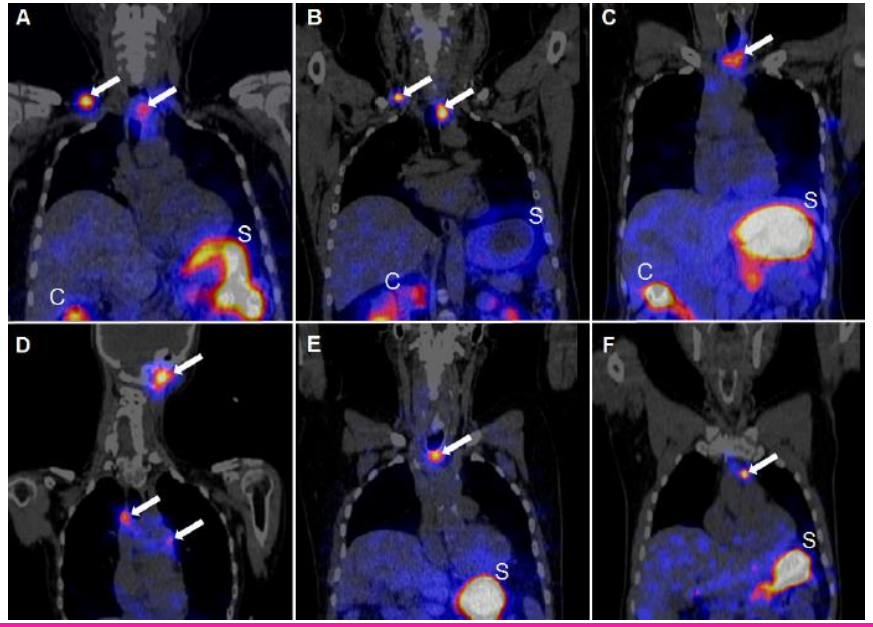
MTC

- PRRT with ^{177}Lu-DOTATATE:
  - only retrospective data of small series
  - 60% have high uptake on SSTR imaging, marked heterogeneity
  - 35-40% SD

- PRRT with ^{177}Lu-PP-F11N (first in human):
  - 90-95% overexpress cholecystokinine-2 receptor
  - specific accumulation with high radiation dose in MTC tissue, potential therapeutic effect



- dosimetry results suggest that the dose limiting organ is the stomach
- nausea, headache, hot flushes during injection

Beukhof C *et al*: *BMC Cancer* 2019, Rottenburger C *et al*: *EJNMMI* 2019

THE CHALLENGE FOR THE NEXT 5-10y

- PERSONALIZATION

  upon risk factors, FDG, dosimetry, predictive biomarkers

- VALIDATION OF NEW STRATEGIES

  combination therapies, intra-arterial, use of alphas

  new theragnostic agents: antagonists, GLP1R

- REGISTRATION and approval in other NETs (not yet in B)

"nothing in life is to be feared
it is only to be understood"

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